

A case of vertical supranuclear gaze palsy

HISTORY

A 31 year old woman presented with a history of poor co-ordination since childhood. During childhood she had been clumsy with frequent falls and had never been able to ride a bike. Her balance progressively deteriorated. By her mid 20s she had developed slurred speech and her family had noted impaired memory. Her falls had been more marked recently. There was no other past history or family history of neurological disease.

EXAMINATION

She was rather disinhibited with poor insight and rather global cognitive dysfunction (MMSE 13/30). Particularly she had reduced attentional, episodic memory and motor sequencing function. She had some athetoid movements of her head and neck, and dystonic movements of her upper limbs and trunk. Eye movements were impaired with an absence of vertical downward saccadic and pursuit movements (see video) which was supranuclear in nature. She had dysarthria, slow tongue movements and a brisk jaw jerk. In the limbs she had bilateral cerebellar signs, but otherwise normal tone, power, reflexes and plantars. General examination was otherwise unremarkable with no hepatic or splenic enlargement.

INVESTIGATIONS

Routine investigations including brain MRI and CSF had been normal. However because of the clinical suspicion of Niemann-Pick type C (NPC), she had bone marrow aspirate, which revealed frequent large histiocytic cells and abundant foamy cytoplasm. Fibroblast cultures and filipin staining confirmed the diagnosis of NPC.

DISCUSSION

Niemann-Pick type C (NPC) is an autosomal recessive lipid storage disorder that affects the viscera and central nervous system. Its phenotype is highly variable but usually onset is in childhood. The slowly progressive form

described in the current case is a rarer manifestation. Common neurological features include dystonia, ataxia, progressive dementia, and the vertical supranuclear gaze palsy is an important diagnostic clue. In general hepatosplenomegaly is milder than in other types of Niemann-Pick. Biochemical diagnosis relies upon an assay of the patient's skin fibroblasts to demonstrate delayed low-density lipoprotein derived cholesterol esterification, and the demonstration of intracellular accumulation of cholesterol using a cytologic technique (filipin staining).

Patients with NPC have mutations in NPC1 or NPC2 gene (18q11-q12). These proteins are involved in cellular post-lysosomal/late-endosomal transport of cholesterol and glycolipids, and it is likely that deficient translocation of cholesterol from lysosomes to other intracellular membrane sites may play an important role in the pathogenesis of NPC.

Until recent times the treatment of NPC has been supportive only. However more recently several drugs have been developed for the related lysosomal disease, Gaucher's. Of these miglustat has shown some promise in animal models of NPC (Zervas et al, 2001; Lachmann, 2003). Miglustat (N-butyldeoxynojirimycin) is an orally active iminosugar which inhibits the biosynthesis of macromolecular substrates that accumulate pathologically in glycosphingolipidoses. Clinical trials are underway to evaluate its use in NPC.

REFERENCES

- Lachmann R (2003) Miglustat *Curr Opin Invest Drugs* 4:472-479
- Zervas M, Somers KL, Thrall MA, Walkley SU (2001) Critical role for glycosphingolipids in Niemann-Pick disease type C *Curr Biol* 11:1283-1287



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